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## Progressive and Interrelated Functional and Structural Evidence of Post-Onset Brain Reduction in Schizophrenia

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### Abstract

**Context**—Progressive brain abnormalities in schizophrenia remain controversial. Evidence of interrelated progressive functional impairment would buttress the case for structural progression. Mismatch negativity (MMN) is reduced in chronic but not first-hospitalized schizophrenia and may index progressive structural changes.

**Objective**—To determine whether MMN shows associations with underlying auditory cortex gray matter at first hospitalization and progressive reduction longitudinally.

**Design**—Cross-sectional (first hospitalization) and longitudinal (1.5-year follow-up).

**Setting**—A private psychiatric hospital.

**Participants**—Protocol entrance: MMN and magnetic resonance imaging at first hospitalization in 20 subjects with schizophrenia, 21 subjects with bipolar disorder with psychosis, and 32 control subjects. Longitudinal electrophysiologic testing: MMN in 16 subjects with schizophrenia, 17 subjects with bipolar disorder, and 20 control subjects. Longitudinal electrophysiologic testing and magnetic resonance imaging: MMN and magnetic resonance imaging in 11 subjects with schizophrenia, 13 subjects with bipolar disorder, and 13 control subjects. At each time point, reported samples were group matched for age, handedness, and parental socioeconomic status.

**Interventions**—Electrophysiologic testing and high-resolution structural magnetic resonance imaging.

**Main Outcome Measures**—Mismatch negativity amplitude and Heschl gyrus and planum temporale gray matter volumes.

**Results**—Initially, groups did not differ in MMN amplitude. Subjects with schizophrenia showed associations between MMN and Heschl gyrus ( $r=-0.52$ ;  $P=.02$ ) not present in the other groups. At longitudinal MMN testing, schizophrenia showed MMN reduction ( $P=.004$ ). Only schizophrenia

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evinced longitudinal left hemisphere Heschl gyrus reduction ( $P=.003$ ), highly correlated with MMN reduction ( $r=0.6$ ;  $P=.04$ ).

**Conclusions**—At first hospitalization for schizophrenia, MMN indexed left hemisphere Heschl gyrus gray matter volume, consistent with variable progression of pre-hospitalization cortical reduction. Longitudinally, the interrelated progressive reduction of functional and structural measures suggests progressive pathologic processes early in schizophrenia. An active process of progressive cortical reduction presents a potential therapeutic target. Mismatch negativity may be a simple, sensitive, and inexpensive index not only of this progressive pathologic process but also of successful intervention.

Schizophrenia is a chronically debilitating disease, typically striking during young adulthood. Approximately 50% of patients will not remain employed even part-time after their first hospitalization.<sup>1</sup> With the cost of treatment and care factored in, the disease has an enormous impact on society. Although most now agree that the bizarre manifestations of schizophrenia stem from brain abnormalities, disagreement about its course exists. Whether schizophrenia includes progressive brain degeneration has been controversial since Kraepelin<sup>2</sup> first chose the name *dementia praecox*, or precocious dementia, for the syndrome. Kraepelin conceived of an early-onset dementing disorder with progressive mental deterioration due to degeneration of the frontal and temporal neocortices. Shortly thereafter Bleuler,<sup>3</sup> renaming the syndrome *schizophrenia*, disagreed with invariable cognitive and structural decline, emphasizing cases with recovery. More than 100 years later, the issue has not been resolved. Whether schizophrenia involves progressive brain change is more than an esoteric issue: Progressive change presupposes an active process that can be targeted pharmacologically before it has completed its insidious attack, whereas static brain lesions reflect the end stage of completed deterioration.

Evidence of prenatal and perinatal complications<sup>4,5</sup> and little evidence of progressive brain degeneration in chronically ill patients<sup>6,7</sup> have argued against a degenerative course in schizophrenia. Dominant theories of schizophrenia propose a static encephalopathy, whereby some early lesion interacts with other areas later during neurodevelopment, causing psychosis.<sup>8</sup> However, several lines of structural and functional evidence indicate greater-than-normal age-related cortical gray matter volume reductions in chronic schizophrenia, including greater-than-normal slowing of event-related brain potentials,<sup>9</sup> greater-than-normal ventricular enlargement,<sup>10</sup> and greater-than-normal gray matter volume reduction.<sup>11,12</sup> Nevertheless, studies of patients with chronic schizophrenia tested long after disease onset have not provided overwhelming evidence of progressive brain abnormalities. In contrast, magnetic resonance imaging (MRI) studies of patients early in the disease process provide greater evidence of progressive changes, including progressively increased ventricle size,<sup>13–16</sup> progressively reduced whole brain volume and whole gray matter,<sup>12,17,18</sup> and progressively reduced frontal gray matter and temporal gray matter as well as increased sulcal cerebrospinal fluid.<sup>12,19,20</sup> Progressive cortical gray matter loss during adolescence in childhood-onset schizophrenia has also been reported.<sup>21,22</sup>

Our group reported marked progressive reductions in left temporal lobe gray matter,<sup>23,24</sup> consistent with data from monozygotic twins discordant for schizophrenia showing marked temporal lobe reductions only in affected twins.<sup>25</sup> After first hospitalization, schizophrenia is characterized by progressive left hemisphere temporal lobe volume reductions. Whether the right hemisphere also shows progressive changes later in the early course of the disease is unknown, but markedly left-lateralized temporal lobe gray matter reductions remain in chronically ill patients with schizophrenia.<sup>26</sup> This sizable left hemisphere cortical gray matter reduction in the first few years after first hospitalization is the strongest empirical evidence of an active degenerative course in schizophrenia. This progressive cortical reduction may be nonlinear, with a circumscribed period of intense cortical reduction surrounding the first

psychotic break abating after a few years.<sup>27,28</sup> Although the structural MRI data present strong evidence of this period of intense degeneration near symptom onset, it has been variable, and the validity of the longitudinal MRI data has been questioned, perhaps being affected by confounds such as between-image differences in brain hydration<sup>29</sup> or medication effects.<sup>13, 30–32</sup>

If schizophrenia involves such a period of progressive cortical gray matter reduction near first hospitalization, then longitudinal testing of first-episode patients should reveal not only progressive reductions of brain structure but also progressive worsening of functional measures of the integrity of the shrinking cortical areas. The presence of interrelated structural and functional abnormalities, via 2 independent methods, would bolster the case for progressive cortical reduction. Auditory mismatch negativity (MMN), a bioelectric brain index of functional echoic memory processes arising mainly from the temporal lobe auditory cortex in and around Heschl gyrus,<sup>33–36</sup> is reduced in chronic schizophrenia<sup>37–39</sup> but not in first-hospitalized patients.<sup>39</sup> We herein provide the first prospective longitudinal evidence of interrelated progressive functional and structural brain abnormalities near schizophrenia onset, reflected in progressive voltage reduction of the MMN brain wave that is strongly correlated with progressive gray matter volume loss in the left hemisphere Heschl gyrus, which contains most, if not all, of the primary auditory cortex.<sup>40,41</sup>

## METHODS

### EVENT-RELATED POTENTIAL RECORDING

Event-related brain potentials were recorded from the scalp according to the method described in detail by Salisbury et al.<sup>39</sup> Briefly, the electroencephalogram was recorded from the scalp from 28 sites, including the standard 10–20 sites and 8 interpolated sites, passed between 0.15 and 40 Hz, and referenced to linked earlobes. Bipolar vertical electro-oculograms (above and below the right eye) and horizontal electro-oculograms (left and right canthi) were also recorded to monitor eyeblinks and movements. Activity exceeding  $\pm 50 \mu\text{V}$  at Fp1/2 or F7/8 was considered artifact and was rejected. Epochs were constructed 50 milliseconds before to 300 milliseconds after a 100-millisecond tone pip (10-millisecond rise/fall) was presented. Tones were presented 3 per second (1600 total) while subjects performed an asynchronous visual checkerboard reversal tracking task. Mismatch negativity amplitude was measured from the midline anterior site (Fz), where it is typically largest. Amplitude was quantified as the mean voltage from 100 to 200 milliseconds in the subtraction waveform constructed by removing the brain activity to standard, repetitive stimuli (1 kHz, 95%) from the brain response to rare, deviant stimuli (1.2 kHz, 5%).

### MAGNETIC RESONANCE IMAGING

Magnetic resonance images were obtained and measured according to the method described in detail by Kasai et al.<sup>24</sup> The primary anatomical structures of interest were the left and right Heschl gyri, containing primary and portions of secondary auditory cortices.<sup>40,41</sup> The planum temporale, the posterior gyrus containing secondary and tertiary auditory association cortices, was also measured bilaterally. Magnetic resonance images were obtained using a 1.5-T scanner (GE Medical Systems, Milwaukee, Wis) using 2 acquisition protocols. A 3-dimensional Fourier transform spoiled gradient-recalled acquisition protocol produced a coronal series of contiguous images (repetition time, 35 milliseconds; echo time, 5 milliseconds; repetitions, 1; nutation angle, 45°; field of view, 24 cm; number of signals acquired, 1.0; and matrix, 256 × 256 [192 phase-encoding steps] × 124). Voxels were 0.9375 × 0.9375 × 1.5 mm. Data were reformatted into isotropic voxels of 0.9375 mm. The second acquisition resulted in an axial series of contiguous double-echo (proton-density and T2-weighted) images used to assess intracranial contents (repetition time, 3000 milliseconds; echo time, 30 and 80 milliseconds;

field of view, 24 cm; and interleaved acquisition with 3-mm slice thickness). Voxels were  $0.9375 \times 0.9375 \times 3$  mm.

## SUBJECTS

Patient recruitment and diagnostic procedures are described in detail by Salisbury et al.<sup>39</sup> Subjects were recruited from McLean Hospital inpatient units at their first hospitalization for psychosis or within 1 year of their first hospitalization for psychosis ( $n=72$ ; range, 0–11 months; mean, 1.7 months; and median, 2 weeks). Provisional research diagnoses were established at protocol entrance via the Structured Clinical Interview for *DSM-IV*, and diagnoses were reassessed at longitudinal testing for subjects who returned for follow-up. This was a fully longitudinal design. Subjects were tested at protocol entrance and again during the early course of their disease. Ideally, all subjects would have completed electrophysiologic and MRI retesting, but some were lost to follow-up. In addition, some subjects who completed retesting were culled to match samples. Patient sample overlap among studies is presented in Figure 1.

For MMN and MRI at protocol entrance, first-hospitalized patients represent a subsample of the patients reported by Salisbury et al.<sup>39</sup> in addition to patients recruited subsequently. At protocol entrance, 16 (22%) of 72 patients refused or could not tolerate MRI. Matched first-episode patients in this analysis were tested 6 months or less from their first hospitalization ( $n=41$ ; range, 0–6 months; mean, 1 month; and median, <1 week) and comprised 20 subjects with first-episode schizophrenia (3 females; mean $\pm$ SD age,  $24.5\pm6.5$  years; mean $\pm$ SD parental socioeconomic status [SES],<sup>42</sup>  $1.85\pm0.9$ ; with 14 receiving atypical neuroleptics, 1 receiving traditional neuroleptics, 3 receiving both, and 2 unmedicated) and 21 subjects with first-episode psychotic bipolar disorder, mania (4 females; mean $\pm$ SD age,  $21.8\pm5.0$  years; mean $\pm$ SD parental SES,  $1.52\pm0.9$ ; with 14 receiving atypical neuroleptics, 1 receiving atypical and traditional neuroleptics, and 6 receiving no antipsychotic medication). A group of 32 psychiatrically well subjects (10 females; mean $\pm$ SD age,  $24.1\pm3.7$  years; mean $\pm$ SD parental SES,  $1.53\pm0.8$ ) from the general population served as controls. Samples did not differ significantly on age, parental SES, or handedness.<sup>43</sup> All groups were above average in intelligence (Wechsler Adult Intelligence Scale–R<sup>44</sup> information subscale, group means >12). Patient samples did not differ in mean $\pm$ SD overall symptom severity as measured using the Brief Psychiatric Rating Scale (BPRS)<sup>45</sup> (first-episode schizophrenia:  $37.3\pm13.2$ ; first-episode psychotic mania:  $32.9\pm10.7$ ;  $P=.25$ ).

Subjects with psychosis were reassessed approximately a year and a half after protocol entrance (specific intervals are reported for each study). Subjects with psychosis lost to follow-up testing (37/72 [51%]) did not differ from retested subjects with psychosis in mean $\pm$ SD age (returned:  $23.3\pm5.4$  years; lost:  $25.2\pm7.8$  years;  $t_{70}=1.2$ ;  $P=.24$ ), total BPRS scores (returned:  $36.1\pm11.7$ ; lost:  $34.1\pm10.0$ ;  $t_{65}=0.8$ ;  $P=.46$ ), medication dosages (returned:  $192.4\pm189.1$ ; lost:  $215.4\pm188.3$ ;  $t_{69}=0.5$ ;  $P>.6$ ), SES (returned:  $3.1\pm1.2$ ; lost:  $3.5\pm1.2$ ;  $t_{67}=1.3$ ;  $P=.20$ ), or parental SES (returned:  $1.7\pm0.8$ ; lost:  $1.9\pm1.2$ ;  $t_{67}=0.6$ ;  $P=.56$ ) measured at protocol entrance. However, subjects with psychosis lost to follow-up had lower mean $\pm$ SD scaled Wechsler Adult Intelligence Scale information scores (returned:  $13.4\pm2.7$ ; lost:  $11.5\pm2.9$ ;  $t_{67}=2.8$ ;  $P=.006$ ), although both groups were well above average in estimated premorbid intellect. Also, subjects with psychosis lost to follow-up had worse social functioning (mean $\pm$ SD Global Assessment of Functioning scale scores: returned:  $37.3\pm8.3$ ; lost:  $31.1\pm8.3$ ;  $t_{66}=3.1$ ;  $P=.003$ ), although both groups had major impairments in several areas of social functioning and reality testing.

All returning subjects with psychosis remained at least mildly impaired at retesting compared with premorbid functioning. Of the 35 subjects with psychosis who returned for retesting, 8 (23%) were inpatients at retesting, and 16 (46%) had been rehospitalized subsequent to protocol entrance. There were no significant differences in MMN amplitudes at retest between subjects

with psychosis rehospitalized ever and those who maintained outpatient status in either patient group.

The first comparison of longitudinal data is for MMN, which more subjects with psychosis tolerated at retest. The mean MMN retest interval did not differ significantly (subjects with schizophrenia, 1.7 years; subjects with bipolar disorder, 1.3 years; and control subjects, 1.4 years;  $F_{2,50}=0.80$ ;  $P=.46$ ). The matched longitudinal MMN retesting subjects with psychosis ( $n=33$ ) were tested within 1 year from their first hospitalization (range, 0–11 months; mean, 1.7 months; and median, <1 week) and comprised 16 subjects with schizophrenia (3 females; mean $\pm$ SD age, 26.4 $\pm$ 8.1 years; mean $\pm$ SD parental SES, 1.8 $\pm$ 0.7) and 17 with psychotic bipolar disorder, mania (2 females; mean $\pm$ SD age, 22.4 $\pm$ 3.6 years; mean $\pm$ SD parental SES, 1.5 $\pm$ 0.7), compared with 20 psychiatrically well control subjects (4 females; mean $\pm$ SD age, 24.5 $\pm$ 4.1 years; mean $\pm$ SD parental SES, 1.4 $\pm$ 0.6). Retest electrophysiologic samples did not differ significantly on age, parental SES, or handedness.

At longitudinal retesting, 5 (14%) of 35 subjects refused or could not tolerate MRI. For combined longitudinal MMN and MRI retesting, the mean MMN retest interval did not differ significantly between groups, but there was a slight trend for subjects with bipolar disorder to have a shorter MMN retest interval (subjects with schizophrenia, 1.7 years; subjects with bipolar disorder, 1.1 years; and control subjects, 1.4 years;  $F_{2,34}=2.63$ ;  $P=.09$ ). The mean MRI retest interval did not differ significantly among groups (subjects with schizophrenia, 1.7 years; subjects with bipolar disorder, 1.3 years; and control subjects, 1.4 years;  $F_{2,34}=0.8$ ;  $P=.46$ ). The matched longitudinal MMN and MRI retesting subjects with psychosis ( $n=24$ ) entered the protocol within 1 year from their first hospitalization (range, 0–11 months; mean, 2.1 months; and median, 2 weeks) and comprised 11 subjects with schizophrenia (2 females; mean $\pm$ SD age, 26.0 $\pm$ 7.9 years; mean $\pm$ SD parental SES, 2.0 $\pm$ 0.6; 4 were taking atypical medications, 4 were noncompliant, and 3 were not prescribed antipsychotic medications by their outside treaters) and 13 subjects with psychotic bipolar disorder, mania (3 females; mean $\pm$ SD age, 22.1 $\pm$ 3.3 years; mean $\pm$ SD parental SES, 1.8 $\pm$ 0.8; 7 were taking atypical medications, 3 were noncompliant, and 3 were not prescribed antipsychotic medications by their outside treaters), compared with 13 psychiatrically well control subjects (4 females; mean $\pm$ SD age, 23.5 $\pm$ 2.7 years; mean $\pm$ SD parental SES, 1.4 $\pm$ 0.7). Samples did not differ significantly on age, parental SES, or handedness.

## ANALYSES

For the analysis of MMN at protocol entrance, groups were compared using 1-way analysis of variance (ANOVA). For the analysis of relative Heschl gyrus volumes (percentage of intracranial contents) at protocol entrance, groups were compared using repeated-measures ANOVA, with hemisphere as the within-subjects factor. Associations between MMN amplitude and Heschl gyrus and planum temporale absolute gray matter volumes were assessed using Pearson correlations. Comparisons of  $r$  values between groups were assessed using directional  $z$ -transforms. For longitudinal MMN testing, repeated-measures ANOVA with diagnosis as the between-subjects factor and time as a within-subjects factor tested for overall effects. Subsequently, nonparametric Wilcoxon signed rank tests were performed to assess longitudinal effects within groups. Wilcoxon signed rank tests rank the magnitudes of differences in each subject, thus preserving the ordinal magnitude of changes while also emphasizing the number of subjects showing a change. This is particularly important if significant change is driven by a subgroup of subjects: to claim that a group of patients shows progressive reductions, most, if not all, should show reduction. Pairwise  $t$  tests within groups were also performed. For combined longitudinal MMN and MRI testing, repeated-measures ANOVA with diagnosis as the between-subjects factor and time as a within-subjects factor tested for overall effects on MMN and on relative Heschl gyrus volumes with the additional



factor of hemisphere. Subsequently, nonparametric Wilcoxon signed rank tests and *t* tests within groups were performed to assess longitudinal effects. To assess the associations between MMN change and absolute left hemisphere Heschl gyrus change, Pearson correlations were used. Change in MMN was calculated as follows: time 1 MMN -time 2 MMN, because MMN is a negative voltage, and Heschl change was calculated as follows: time 2 volume – time 1 volume. Thus, negative change scores mean worsening. Comparisons of *r* values between groups were assessed using directional z-transforms. The distributions of change scores in each group were compared with random distributions using the  $\chi^2$  goodness-of-fit test to determine whether groups differed from random distributions.

## RESULTS

The MMN and Heschl gyrus values for each study are given in the Table. Study 1 examined MMN and Heschl gyrus gray matter volumes cross-sectionally at first hospitalization for psychosis. First-hospitalized subjects with schizophrenia, first-hospitalized subjects with bipolar disorder, and psychiatrically well control subjects did not differ in MMN amplitude at initial testing ( $F_{2,70}=1.2$ ;  $P=.30$ ). Groups differed in relative Heschl gyrus gray matter volumes ( $F_{2,70}=5.8$ ;  $P=.005$ ), and all groups had larger gray matter volumes in the left hemisphere (side:  $F_{1,70}=18.1$ ;  $P<.001$ ). Follow-up ANOVA revealed that first-hospitalized subjects with schizophrenia had reduced relative Heschl gyrus gray matter volumes relative to controls ( $F_{1,50}=11.7$ ;  $P=.001$ ) and relative to first-hospitalized subjects with bipolar disorder ( $F_{1,39}=6.9$ ;  $P=.01$ ). Psychiatrically well controls and first-hospitalized subjects with bipolar disorder did not differ in relative Heschl gyrus gray matter volumes ( $F_{1,51}=0.2$ ;  $P=.89$ ). Subjects with schizophrenia showed a significant association between MMN amplitude at the mid-frontal site (where it is largest) and their left hemisphere Heschl gyrus gray matter volume ( $r=-0.52$ ;  $P=.02$ ) (Figure 2). Pairwise directional z-transform comparisons indicated that the association between MMN and left Heschl gyrus gray matter volume in first-hospitalized subjects with schizophrenia was significantly different from the association in the other groups ( $P<.05$  for all). In schizophrenia, the association between MMN and left hemisphere Heschl gyrus gray matter volumes was different from the correlation in the right hemisphere ( $-0.18$ ) at trend level ( $P=.06$ , Fisher z-transform), and no associations with the left or right planum temporale were apparent. There were no significant associations between MMN and any region of interest in the other groups. However, these cross-sectional data are only indirect evidence of an active period of brain reduction in schizophrenia near first hospitalization and can alternately be explained by variable severity of perinatal insult. Only prospective longitudinal testing from first hospitalization can definitively demonstrate a progressively worsening abnormality.

Study 2 examined MMN longitudinally. Groups did not differ in overall MMN amplitudes ( $F_{2,50}=0.63$ ;  $P=.54$ ). However, groups showed different changes in MMN amplitudes over time (group  $\times$  time,  $F_{2,50}=4.97$ ;  $P=.01$ ). Only subjects with schizophrenia showed progressive reductions in MMN (Figure 3). Wilcoxon signed rank tests revealed that 14 of 16 subjects with schizophrenia showed smaller MMN amplitudes at retest ( $Z=2.9$ ;  $P=.004$ ). By contrast, 8 of 17 subjects with bipolar disorder ( $Z=0.2$ ;  $P=.83$ ) and 12 of 20 control subjects showed MMN reduction ( $Z=0.5$ ;  $P=.60$ ), essentially chance. These findings were confirmed using within-group *t* tests, where subjects with schizophrenia showed significant MMN reductions ( $t_{15}=3.4$ ;  $P=.004$ ) but those with bipolar disorder ( $t_{16}=0.4$ ;  $P=.73$ ) and control subjects ( $t_{19}=1.1$ ;  $P=.27$ ) did not.

Study 3 examined subjects receiving both MMN and MRI longitudinal testing. Groups did not differ in overall MMN amplitudes ( $F_{2,34}=2.16$ ;  $P=.13$ ), and there were significantly different changes in MMN over time in the groups (group  $\times$  time,  $F_{2,34}=6.06$ ;  $P=.006$ ). Wilcoxon signed rank tests revealed that 10 of 11 subjects with schizophrenia showed smaller MMN amplitudes

at retest ( $Z=2.8$ ;  $P=.004$ ), whereas only 6 of 13 subjects with bipolar disorder ( $Z=0.04$ ;  $P=.97$ ) and 7 of 13 control subjects ( $Z=0.5$ ;  $P=.60$ ) showed MMN reduction. These findings were confirmed using within-group  $t$  tests, in which subjects with schizophrenia showed significant MMN reductions ( $t_{10}=5.2$ ;  $P<.001$ ) but those with bipolar disorder ( $t_{12}=0.12$ ;  $P=.90$ ) and control subjects ( $t_{12}=0.85$ ;  $P=.41$ ) did not. For Heschl gyrus gray matter volumes, groups did not differ in relative gray matter volumes ( $F_{2,34}=0.97$ ;  $P=.39$ ), but there were significantly different changes in gray matter over time in the groups restricted to 1 hemisphere (group  $\times$  hemisphere  $\times$  time interaction,  $F_{2,34}=4.88$ ;  $P=.01$ ). Separate ANOVAs isolated the differential changes to the left hemisphere (group  $\times$  time interaction,  $F_{2,34}=4.52$ ;  $P=.02$ ), not the right (group  $\times$  time interaction,  $F_{2,34}=0.86$ ;  $P=.43$ ). Wilcoxon signed rank tests revealed that 11 of 11 subjects with schizophrenia showed reduction ( $Z=2.9$ ;  $P=.003$ ). In contrast, only 6 of 13 subjects with bipolar disorder ( $Z=1.2$ ;  $P=.25$ ) and 8 of 13 control subjects ( $Z=0.1$ ;  $P=.92$ ) showed reduction, essentially chance. These findings were confirmed using within-group  $t$  tests, in which subjects with schizophrenia showed significant left Heschl gyrus gray matter reductions ( $t_{10}=4.5$ ;  $P<.001$ ) but those with bipolar disorder ( $t_{12}=1.47$ ;  $P=.17$ ) and control subjects ( $t_{12}=0.05$ ;  $P=.96$ ) did not.

Of primary importance was the tight interrelationship between the progressive reductions of MMN amplitude and left hemisphere Heschl gyrus gray matter volumes in schizophrenia. These reductions were highly correlated in subjects with schizophrenia ( $r=0.62$ ;  $P=.04$ ) but not in those with psychotic bipolar disorder or control subjects (Figure 4). In the schizophrenia group, the correlation between left hemisphere cortical gray matter change and MMN change was different from the correlation between right hemisphere change and MMN change ( $-0.12$ ), attaining marginal significance ( $P=.06$ ). Recall, however, that right Heschl gyrus volumes showed no significant change over time. The association between MMN decrement and left Heschl gyrus gray matter volume decrement in subjects with schizophrenia was significantly different from the association in the other groups ( $P<.05$  for all). No significant associations with the left or right planum temporale were apparent. Furthermore, nearly all of the subjects with schizophrenia were in the quadrant defined by both MMN reduction and Heschl gyrus reduction. Assuming a chance distribution around the 2 dimensions, the expected random distribution would be 25% per quadrant. Neither control subjects nor those with bipolar disorder differed significantly from a random distribution ( $\chi^2<1$  in each group;  $P>.8$  for all). By contrast, subjects with schizophrenia were extremely different from a random distribution ( $\chi^2=23.6$ ;  $P<.001$ ).

## COMMENT

Several results support the presence of an active period of peri-onset cortical reduction in schizophrenia. At first hospitalization, only subjects with schizophrenia showed an abnormal brain volume–brain activity correlation between left hemisphere Heschl gyrus gray matter cortical volume and MMN amplitude, despite normal group mean amplitude and gray matter volume. This is consistent with a similar association between MMN and Heschl gyrus volume in chronic schizophrenia.<sup>46</sup> Subjects with psychotic bipolar disorder and control subjects likely had substantially more cortex than necessary to generate MMN and, hence, no statistical relationship between the size of their cortex and the size of their electrical response. The abnormal brain structure–function relationship at first hospitalization is consistent with progressive cortical reduction before the emergence of psychotic symptoms and cannot be explained by medication effects because most subjects were only acutely medicated after hospitalization. However, subjects with abnormally small MMN and Heschl gyrus volumes may well have had those abnormalities from birth, and only longitudinal testing can prove progressive reductions.



Longitudinal testing of MMN showed that nearly all subjects with schizophrenia showed MMN amplitude reduction and left hemisphere Heschl gyrus gray matter volume reduction. Of primary importance was a tight relationship between MMN reduction and gray matter loss. Highly related progressive abnormalities of functional and structural measures are present in schizophrenia after the first hospitalization. Therefore, MMN at initial hospitalization may serve as an index of the course of prehospitalization brain reduction in schizophrenia, and MMN subsequently may index continued cortical volume reduction.

Our ideas about the causes and course of schizophrenia need be readdressed. In the static lesion model of schizophrenia, which has been highly influential, prenatal or perinatal developmental abnormalities or insults form a primary static lesion with emergence of symptoms in young adulthood due to dysfunction of brain areas maturing later in life.<sup>8</sup> Alternative theories of combined early static and late progressive lesions have been proposed (eg, see Waddington et al<sup>47</sup> and Pantelis et al<sup>48</sup>), wherein the prenatal or perinatal neurodevelopmental abnormality interacts with some form of late-adolescent cortical gray matter reduction synergistically to cause psychosis. The MRI and MMN data from this study support the presence of a late progressive lesion.

The underlying biological mechanism of this late lesion is unknown. The schizophrenic brain as revealed through postmortem histologic examination is characterized by increased cell density,<sup>49</sup> smaller somal size,<sup>50</sup> reductions in the dendritic spines<sup>51</sup> in the tertiary frontal cortex, and smaller somal size<sup>52</sup> in the temporal cortices. These data indicate that schizophrenia is not characterized by classic neural degeneration but rather by a process of neuronal volume reduction that primarily involves dendrites.<sup>53,54</sup> Several candidate mechanisms for this reduction in dendrites have been suggested, including glutamatergic excitotoxicity<sup>55–57</sup> and synaptogenesis abnormalities.<sup>56,58</sup>

If glutamate plays a role in the late progressive lesion, there may be good reason why MMN seems to be a sensitive index of this process. Mismatch negativity reflects current inflow in *N*-methyl-D-aspartate glutamate receptors<sup>59</sup> and is reduced in healthy individuals after *N*-methyl-D-aspartate antagonists.<sup>60</sup> The relationship among MMN, *N*-methyl-D-aspartate glutamate receptors, and dendrite physiology may be especially important for understanding the brain abnormalities of schizophrenia. The association between MMN and progressive gray matter volume reduction has novel clinical implications; early pharmacologic intervention to prevent progressive cortical gray matter reduction may be tracked via the relatively noninvasive measurement of MMN amplitude.

Several caveats should be considered. Retest MRI may be confounded by changes in hydration and perfusion between images,<sup>29</sup> and medication may be associated with changes in cortical volumes, equivocally both increases<sup>30</sup> and reductions.<sup>31,32</sup> Subjects in this study were generally taking atypical medications, recently related to less cortical gray matter reduction.<sup>31</sup> Comparison of subjects with schizophrenia who were taking atypical medications at follow-up with those who were not revealed no significant differences in Heschl gyrus volume loss (effect size  $d = 0.23$ ) or MMN reduction (effect size  $d = 0.37$ ). Subjects who were taking atypical antipsychotics and those who were not showed cortical gray matter and MMN reduction, with relatively small effect sizes for increased loss if not medicated at all. In addition, testing of subjects with psychotic bipolar disorder who were receiving antipsychotic medications served as a natural control for medication effects, and those subjects showed no evidence of MMN or Heschl gyrus reductions. Furthermore, medication effects would be expected to be observed across the whole brain, yet the left, but not the right, Heschl gyrus was reduced in these subjects. These data weigh against any global hydration, perfusion, or medication effects. Second, subjects with schizophrenia lost to follow-up may differ significantly in terms of course from those who returned. There were moderately lower IQ and worse Global Assessment of

Functioning scale scores in the lost subjects. However, both groups were relatively bright and significantly impaired. Third, other brain areas may show progressive reductions that correlate with MMN. We note that MMN generators are not distributed throughout the brain, and the temporal lobe accounts for much, if not all, MMN activity. Fourth, the single-rater intraclass correlations for Heschl gyrus volumes were high in all groups (subjects with schizophrenia, 0.96; subjects with bipolar disorder, 0.97; and control subjects, 0.93), but MMN reliabilities were lower (schizophrenic subjects, 0.74; bipolar subjects, 0.22; and control subjects, 0.52). We note that the schizophrenia group, where the main finding is present, was acceptably reliable. State effects might account for the low MMN reliability in subjects with bipolar disorder. Never re-hospitalized subjects with bipolar disorder ( $n=11$ ) showed an increase in MMN amplitudes ( $\sim 27\%$ ), and those ever rehospitalized ( $n=9$ ) showed a reduction ( $\sim 20\%$ ). Finally, there were no associations between negative symptoms and MMN amplitudes at either time 1 or time 2, as has been reported in chronic schizophrenia.<sup>61</sup> Likewise, we did not detect any associations between MMN amplitudes and social functioning.<sup>62</sup> We suspect that the changing clinical picture of first-episode patients likely plays a role in this lack of associations. First-hospitalized patients have not settled into a characteristic pattern or typical constellation of symptoms and present with extreme anxiety and turmoil in a state of symptom flux and evolution. Thus, the clinical and social functioning measures may have a relative emphasis on state rather than trait. We note that significant associations in the first-hospitalized schizophrenic subjects between anxiety at time 1 and subsequent MMN change ( $r=-0.58$ ;  $P=.06$ ) and Heschl change ( $r=-0.77$ ;  $P=.005$ ) highlight the unique clinical picture at protocol entrance. Furthermore, there was no association between anxiety at retest and MMN or Heschl gyrus change. At retesting a significant association between paranoia and MMN reductions emerged. Subjects with schizophrenia with the most paranoia at retest had the greatest MMN amplitude reductions ( $r=-0.65$ ;  $P=.03$ ), although the association with Heschl gyrus volume reduction did not attain significance ( $r=-0.4$ ;  $P=.25$ ).

In summary, these interrelated functional and structural measures support the presence of a late progressive lesion in schizophrenia. Mismatch negativity amplitude in schizophrenia, even when within the normal range, is tightly coupled to the volume of the underlying left temporal auditory cortex, shows progressive reductions coupled with ongoing cortical gray matter reduction of the left temporal auditory cortex, and, thus, may serve as a metric of successful interventions in halting such peri-onset progressive abnormalities.

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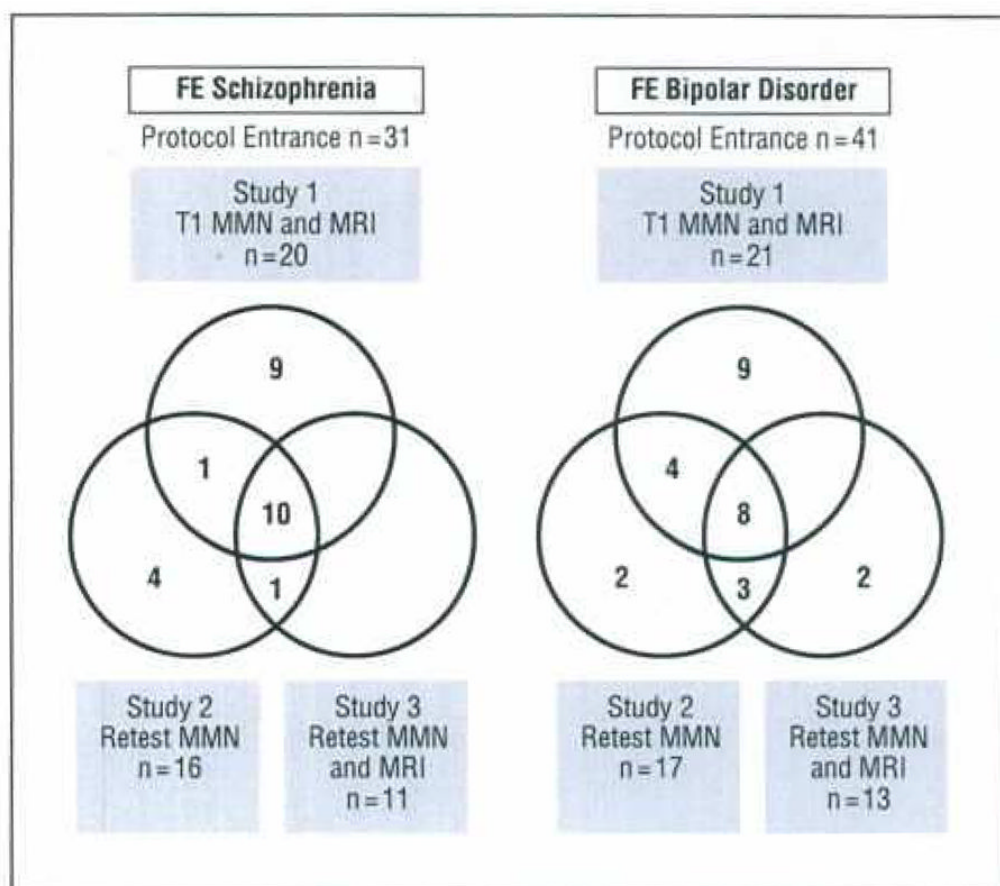
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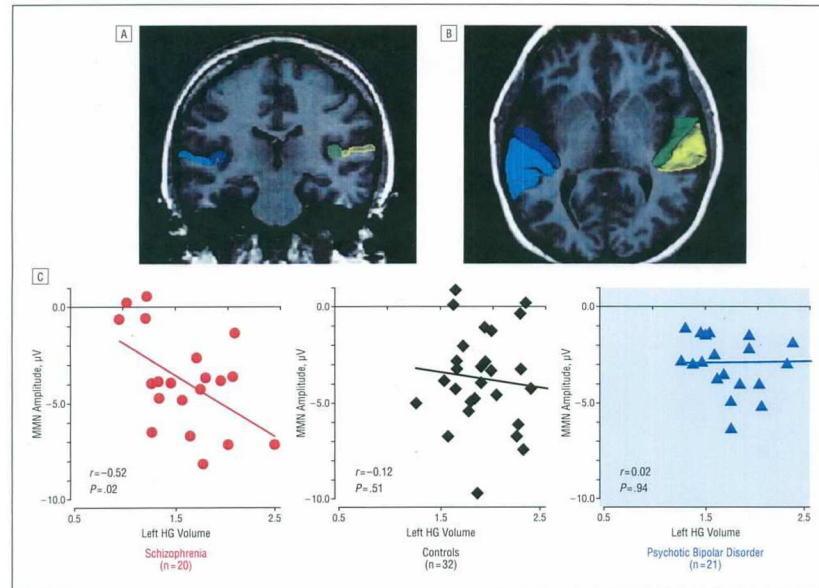
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**Figure 1.**

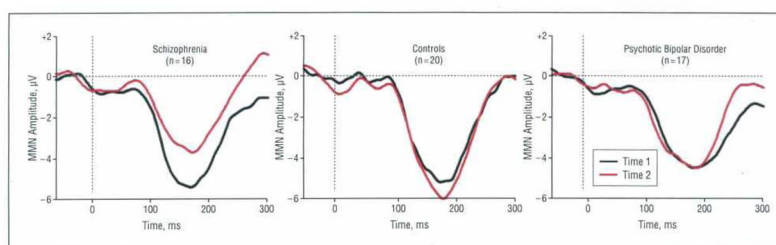
Venn diagram of the patient sample overlap among the 3 studies. FE indicates first-episode; MMN, mismatch negativity; MRI, magnetic resonance imaging; and T1, time 1.



**Figure 2.**

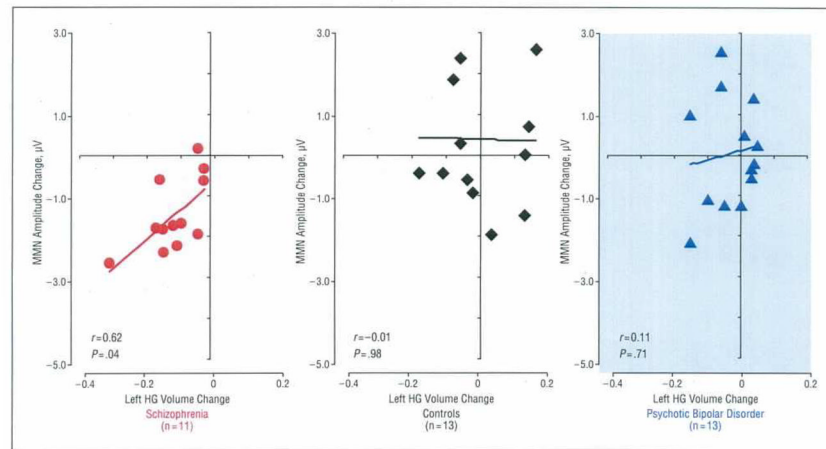
Magnetic resonance imaging–defined regions of interest and correlations with mismatch negativity (MMN) at first hospitalization.

A and B, Three-dimensional magnetic resonance imaging constructions of major subdivisions of the superior temporal plane. Heschl gyri (dark blue and dark green) mainly contain the primary auditory cortex. The planum temporale (light blue and yellow-green) contains secondary and tertiary auditory association cortices. The left side of the figure is the left hemisphere. Note the larger left hemisphere planum temporale. C, At first hospitalization, despite mean MMN amplitudes within the normal range, subjects with schizophrenia showed an abnormal relationship between MMN and underlying left hemisphere primary auditory cortex volumes, consistent with some degree of prehospitalization cortical volume reductions in some subjects with schizophrenia. HG indicates Heschl gyrus; colored lines, regression line.



**Figure 3.**

At longitudinal retesting, subjects with schizophrenia, who showed normal mean mismatch negativity (MMN) initially, now show significant reduction in MMN. Control subjects and subjects with bipolar disorder showed essentially no change in MMN amplitude.



**Figure 4.**

Relationship of mismatch negativity (MMN) amplitude reduction and left hemisphere primary auditory cortex gray matter volume loss. Whereas the subjects with bipolar disorder and control subjects cluster around 0 in both MMN amplitude change and gray matter change, those with schizophrenia are almost exclusively contained in the negative quadrant defined by MMN reduction and gray matter loss. HG indicates Heschl gyrus; colored lines, regression line.

Table

MMN Amplitudes and Absolute MRI Volumes\*

	MMN Time 1	MMN Time 2	MMN Change	Left HG Time 1	Left HG Time 2	Left HG Change	Right HG Time 1	Right HG Time 2	Right HG Change
Protocol entrance									
Schizophrenia (n = 20)	-3.84 ± 2.54	NA	NA	1.61 ± 0.39	NA	NA	1.41 ± 0.38	NA	NA
Psychotic bipolar disorder (n = 21)	-2.88 ± 1.50	NA	NA	1.83 ± 0.44	NA	NA	1.68 ± 0.50	NA	NA
Controls (n = 32)	-3.82 ± 2.67	NA	NA	2.02 ± 0.40	NA	NA	1.66 ± 0.37	NA	NA
MMN follow-up									
Schizophrenia (n = 16)	-4.25 ± 2.72	-2.84 ± 1.89	-1.41 ± 1.65	NA	NA	NA	NA	NA	NA
Psychotic bipolar disorder (n = 17)	-3.32 ± 1.55	-3.51 ± 2.72	0.19 ± 2.24	NA	NA	NA	NA	NA	NA
Controls (n = 20)	-3.80 ± 1.87	-4.18 ± 1.40	0.38 ± 1.50	NA	NA	NA	NA	NA	NA
MMN and MRI follow-up									
Schizophrenia (n = 11)	-4.35 ± 2.32	-2.90 ± 1.92	-1.46 ± 0.94	1.83 ± 0.50	1.72 ± 0.48	-0.113 ± 0.08	1.57 ± 0.51	1.56 ± 0.48	-0.01 ± 0.05
Psychotic bipolar disorder (n = 13)	-3.04 ± 1.20	-3.08 ± 0.93	0.05 ± 1.35	1.78 ± 0.28	1.78 ± 0.28	-0.001 ± 0.12	1.76 ± 0.32	1.73 ± 0.33	-0.04 ± 0.08
Controls (n = 13)	-4.09 ± 1.86	-4.47 ± 1.44	0.39 ± 1.63	1.80 ± 0.37	1.76 ± 0.32	-0.03 ± 0.07	1.86 ± 0.33	1.82 ± 0.34	-0.05 ± 0.06

Abbreviations: HG, Heschl gyrus; MMN, mismatch negativity; MRI, magnetic resonance imaging; NA, not applicable.

\* Data are given as mean ± SD.